Lilly

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April 15, 1999

Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Re: [Docket No. 98D-1267] Guidance for Industry; *NDAs: Impurities in Drug Substances*, December 1998 (Comments due April 21, 1999)
Federal Register: January 21, 1999 (Volume 64, Number 13)]

Dear Madam or Sir:

Eli Lilly and Company is pleased to have the opportunity to provide comments on the draft guidance for industry, *NDAs: Impurities in Drug Substances*, December 1998.

Please feel free to contact me at (317)276-0368 for clarification of any comments.

Sincerely,

Tobias Massa

Tobias Massa, PhD.
Director, Global Regulatory Affairs,
Chemistry Manufacturing and Control

98D-1267

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A. General Comments:

FDA notes in the subject guidance that ICHQ3A was developed to provide guidance for **new** drug substances, but believes it applies to drug substances which are **not** new. We disagree with this belief. We believe that the ICH process provides an appropriate scientific forum to develop guidance in accordance with the scope intended, but extrapolation beyond the intended purpose is inappropriate. We recommend that any overarching guidance on impurities for existing drug substances or drug products should be discussed in the ICH forum in order to develop a harmonized, scientifically based guidance.

We consider the scope of the application of ICH Q3A principles as referenced in BACPAC I to provide an appropriate and adequate approach to evaluating changes to an existing drug substance synthesis or process. Additional requirements in ICH Q3A (as detailed below) go beyond what is necessary to ensure public safety.
Likewise, unless a new dosage form of an existing drug substance would increase the maximum daily dosage or exposure of the drug substance significantly, the impurity limits in place for the drug substance should be sufficient. These limits have proven safe through clinical trials and use in the general population. Analyzing the existing drug substance retrospectively and establishing new specifications would provide no additional benefit to the public.
We therefore encourage the agency to discontinue the finalization of the guideline *NDAs: Impurities in Drug Substances* and continue instead to work with industry in finalizing the BACPAC guidance documents.

B. The following requirements from ICHQ3A are unnecessary for existing drug substances and, additionally, are inconsistent with the draft guidance provided in BACPAC I.

Identification and Characterization of Impurities:
ICHQ3A requires that:

> The applicant should summarize those actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance....
> The studies conducted to characterize the structure of actual impurities present in the new drug substance at or above an apparent level of 0.1% (e.g., calculated using the response factor of the drug substance) should be described.....
> Identification of all recurring impurities at or above the 0.1% level is expected in batches manufactured by the proposed commercial process.

We note that BACPAC I more appropriately requires that "no new impurities are present at or above the threshold for qualification of impurities (*per ICHQ3A*) with existing impurities being within the stated limits or, if not specified, at or below the upper statistical limit of historical data".

By applying the full scope of the ICHQ3A guideline, an applicant would be required to retrospectively identify and characterize impurities which have always been present in the drug substance. If the impurities remain the same, and at or below the levels proven safe through use in the general population, retrospective efforts to characterize or identify those impurities are unnecessary.

Impurity Specifications:

ICHQ3A requires that:

> Specific identified impurities should be included along with recurring unidentified impurities estimated to be at or above 0.1%.....
> Finally, a general specification limit of not more than 0.1% for any unspecified impurity should be included.

We note that BACPAC I more appropriately requires that "no new impurities are present at or above the threshold for qualification of impurities (per ICHQ3A) with existing impurities being within the stated limits or, if not specified, at or below the upper statistical limit of historical data".

By applying the full scope of the ICHQ3A guideline, the applicant may be forced to establish new specifications which do not represent the quality of material which has proven safe through use in the general population.

C. The guidance states that "this recommendation would not apply to DMFs cited in an NDA or supplement if the DMF information has been deemed acceptable prior to the publication of the final version of this guidance". This philosophy is not scientifically sound in that information already submitted in an NDA for a drug substance, which was acceptable previously, would no longer be acceptable in conjunction with a new dosage form or combination product. There is no reason that the mechanism of submitting the information (i.e. DMF vs. NDA) should affect the scientific acceptability of the information. We encourage the agency not to apply the ICHQ3A principles retrospectively in either case.